Editorial

Antiviral drugs and influenza prophylaxis

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Vaccination is the most effective form of protection against influenza. The primary role of neuraminidase inhibitors such as oseltamivir and zanamivir is the treatment of symptomatic infection as their prophylactic benefit is largely restricted to specific risk groups or settings.

Influenza A is a fragile but highly infectious RNA virus which continually re-enters the human population by one of two means. The first is by the mutation of strains that are already present in the human population. These altered strains survive by evading our adaptive immunity and cause seasonal epidemics which affect between 5% and 15% of the population every year. Most strains are not highly virulent but infections result in up to 2500 deaths in Australia each year. The majority of fatalities are in people over 65 years of age and those with significant respiratory, cardiac or renal impairment.

The second means of entry is from an animal reservoir. Migratory water birds such as ducks and geese can spread new influenza A genotypes to domestic fowl and other animals.

In this issue…

Autumn is a time for influenza immunisation. Although the vaccine is usually given to people who are vulnerable to the complications of influenza it may be requested by healthy people. Paul Dugdale examines whether or not immunising healthy people is beneficial. Despite the stockpiling of antiviral drugs to deal with avian influenza, David Siebert says that vaccines will offer more effective prophylaxis.

Anticoagulation is effective prophylaxis after deep vein thrombosis, but recurrent thrombosis can be difficult to diagnose. Harry Gibbs recommends a duplex ultrasound scan when warfarin therapy is completed.

Warfarin is one drug for which brand substitution is not recommended, however there are generic equivalents for many other drugs. Andrew McLachlan, Iqbal Ramzan and Robert Milne dispel some of the myths about bioequivalence and the risks of generic drugs.

An avian outbreak may produce variants that infect humans through contact with the faeces of sick birds. At least one major re-assortment (antigenic shift) of the genes for the viral surface proteins (H and N antigens) is required to produce forms virulent to non-immune humans. If these new variants have or acquire additional mutations that allow efficient human-to-human transmission, a global human epidemic (a pandemic) may ensue.

There have been three pandemics in the last 100 years. In 1918 the 'Spanish flu' killed approximately 2.5% of those it infected – more than 20 million people. This was up to fifty times more virulent than the subsequent pandemics in 1957 and 1968.

The influenza A epizootic H5N1, currently in wild and domestic fowl (bird flu), appears to be highly virulent. Half of the documented human cases have been fatal. Viral derivatives that establish human-to-human transmission may be less lethal if their virulence is sacrificed for transmission efficiency, but we cannot predict their virulence. Since 30–80% of current H5N1 isolates from infected patients are resistant to amantadine, neuraminidase inhibitors are both the first-line treatment and the first choice for prophylaxis in unvaccinated people exposed to the new virus.[1]

The efficacy of neuraminidase inhibitors in the treatment of severe H5N1 infections has been discouraging. This is often due to the long interval between the recognition and treatment of human infections. Early treatment appears to be beneficial.[2] The H5N1 virus can spread beyond the respiratory tree in some people. Shedding can occur at up to 10 times the rate of endemic viruses and may be prolonged for several days. This makes the duration of acute treatment difficult to gauge, but animal studies show that it may have to be for at least 10 days. Inhaled zanamivir is untried and may only be suited to prophylaxis.

In the prophylaxis of influenza, neuraminidase inhibitors are no more than 35–75% effective. The efficacy of oral oseltamivir 75 mg daily against symptomatic influenza is 61%, or 73% for 150 mg daily. This benefit is statistically independent of the dose used. Inhaled zanamivir 10 mg daily is 62% efficacious.[3] By contrast, vaccination against endemic human influenzas is 70–90% effective depending on the antigenic 'match' with the circulating strain.[4,5]

In institutional settings such as nursing homes oseltamivir is up to 92% effective as a prophylactic drug. It has also been shown to prevent lower respiratory tract complications in laboratory proven influenza cases.

Neither oseltamivir or zanamivir prevents asymptomatic infection nor do they have any prophylactic benefit in patients with 'influenza-like illnesses'. Viral resistance to both drugs is relatively uncommon so the lack of prophylactic efficacy appears to be due to other factors.[1] The most common adverse effect is dose-dependent nausea from oseltamivir.

Prophylactic drugs are inherently inferior to vaccines because of the continual need to re-supply, distribute and manage their use. In addition, viral characteristics, such as virulence, transmissibility and drug susceptibility, change in the face of the selection pressure caused by drug use. Judicious use of drug prophylaxis will not prevent pandemic spread, but it can buy time to manage the rate at which outbreaks take hold, allowing the scale-up of vaccine production. While vaccine production is technically difficult and will take a minimum of three months to activate, once there is an effective product, one or two doses will provide a high degree of protection.[6]

Due to the limited size of prophylactic drug stockpiles and their relatively low efficacy compared with vaccines, there are two drug strategies that make sense for managing a pandemic. First, confine the use of stockpiled drugs to the treatment of index cases and limited prophylactic courses for key personnel, including front-line healthcare workers and emergency service providers. Secondly, deploy drugs to interrupt early local transmission. 'Ring-fencing' and extinguishing minor outbreaks are possible, if the basic reproductive number (R_0*) is not high. This may be most valuable where a partially protective vaccine is available or partial immunity develops in the population.

Any strategy for the deployment of these drugs must be inferred from the known research and epidemiological data as prophylactic drug trials will be of limited power while the transmission rate remains low.[2,7]

Effective personal hygiene has a role in preventing the spread of disease, especially in hospital and occupational settings where hand washing and protective clothing are used. Although hygiene and public health measures are less effective in containing the spread of the virus in the general population they will be an important addition to prophylactic drug strategies.

Antivirals will be adjuncts to an effective vaccine, provided one becomes available soon after human-to-human transmission is identified. Unfortunately, only wealthy countries will have access to drug stockpiles and the capacity to expand the production of antiviral drugs and vaccines.

* In general population theory, R_0 describes the expected number of new infected hosts that one infected host will produce during his or her period of infectivity, in a large population that is fully susceptible.

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Further reading

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